COMMUNICATION

Polymer-supported hypervalent iodine reagents in 'clean' organic synthesis with potential application in combinatorial chemistry

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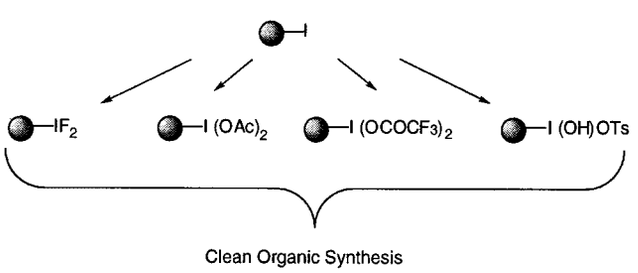
A clean oxidation reaction of a variety of substrates using polymer-supported (diacetoxyiodo)benzene (PSDIB) which proceeds in high to excellent yield with maximum purity is described including isolation and regeneration of the polymer reagent.

The pharmaceutical and agrochemical industries need an ever increasing number of compound libraries to shorten the time taken to identify potential market candidates. At present, the most popular way that this can be achieved is by the use of solid phase organic synthesis (SPOS). To compliment this strategy we have focussed our attention on the development of *orchestrated multi-step synthesis* using polymer-supported reagents for organic synthesis. Although an extensive range of solid and polymer-supported reagents have been described[1a–d] it is only recently that their use in combinatorial chemistry has been realised.[2a–e] We have also successfully implemented polymer-supported reagents in the orchestrated multi-step organic synthesis of heterocycles from simple commercially available monomer building blocks employing sequestering agents to assist reaction clean up.[3–5] These syntheses adequately illustrate the advantages of polymer-supported reagent synthesis but in each of these syntheses, the reagents are generally employed to effect only a single transformation. We therefore investigated the use of polymer-supported reagents which are capable of performing a wide-variety of oxidative functional group transformations which could have multiple use in the generation of compound libraries.

For this reason polymer-supported hypervalent iodine reagents should be ideal candidates due to their known diverse chemistry in solution.[6] Added advantages to these reagents include their low toxicity, mild conditions for use and high selectivities in their reactions all of which rendered them ideal to incorporate into our immobilised reagent programme. In this communication we wish to report our preliminary results using polymer-supported (diacetoxyiodo)benzene (PSDIB) for clean organic synthesis. We have also prepared other polymer-supported iodine reagents (Scheme 1) and demonstrated their



Scheme 1 New polymer-supported hypervalent iodine reagents.

potential in synthesis and these results will be reported at a later date.

Although the preparation of polymer-supported (diacetoxyiodo)benzene (PSDIB) was known[7] its application was limited to a single reaction, that of iodination of electron-rich aromatics and subsequent oxidative 1,2-aryl migration. This report encourages us to declare our observations on the application of polymer-supported (diacetoxyiodo)benzene (PSDIB) emphasising the versatility of this reagent in oxidative reactions and introducing its potential in catalytic synthesis *via* reagent recycling.

As previously described[8] poly(iodostyrene) (PIS), the pivotal intermediate for preparing a family of polymer-supported hypervalent iodine reagents, was prepared by treating commercially available polystyrene with a mixture of iodine, periodic acid and sulfuric acid. Elemental analysis revealed the resin loading to be 3.5 mmol g^{-1} indicating that 76% of the aromatic rings had been successfully iodinated. This highly valuable intermediate was then quantitatively converted into the requisite polymer-supported (diacetoxyiodo)benzene (PSDIB) by treatment with freshly prepared peracetic acid at 40 °C overnight. The resin product was precipitated with ether, collected by filtration, washed with ether, and then dried under vacuum to afford the polymer-supported (diacetoxyiodo)-benzene (PSDIB) with a loading of 3.5 mmol g^{-1}. The resin product was best stored away from direct sunlight and in a refrigerator, although no appreciable decomposition was observed at room temperature.

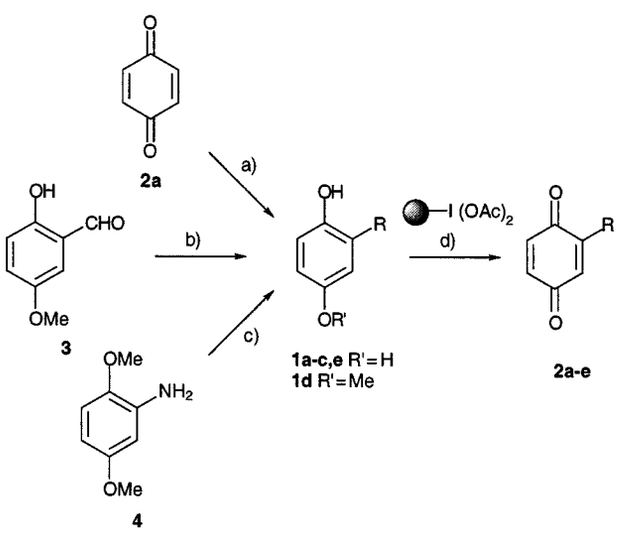
First we examined the oxidation of quinols **1a**–**e** to afford the quinones **2a**–**e** using PSDIB. Quinones are important compounds and are widely distributed in nature. However, not so many substituted hydroquinones (quinols) are commercially available and we therefore had to prepare compounds **1c**–**e** using standard methods. The hydroquinone **1c** was obtained in 85% yield by an efficient 1,4-addition reaction of thiophenol with benzoquinone **2a** in the presence of LiCl in HMPA. The alcohol **1d** was formed in 91% yield by reduction of the appropriate aldehyde **3** with sodium borohydride and the acetanilide **1e** was formed in near quantitative yield, in two steps, by treatment of the aniline **4** with acetyl chloride followed by a facile demethylation reaction effected with BBr_3 at −78 °C in DCM. The five quinols **1a**–**e** were then subjected to oxidation with PSDIB using our general reaction protocol (Scheme 2).[9] Initially we examined the oxidation of the quinols **1a**–**e** using a stoichiometric amount of PSDIB resin in DCM. It was found that these reactions proceeded to virtual completion at room temperature in a few hours and using excess resin, complete conversion to the products **2a**–**e** could be achieved, as judged by LCMS and NMR spectroscopic analysis, which avoided chromatography and only required filtration to afford pure products. The results are summarised in Table 1.

Regeneration and recycling of the iodinated resin was examined on the facile hydroquinone to benzoquinone oxidation reaction (Scheme 3). After the first oxidation the resin was recovered in quantitative yield by suspending in DCM adding ether followed by filtration. The recovered resin was then reoxidised with peracetic acid in the usual manner and the oxidative reactions were repeated with *no loss of activity*.

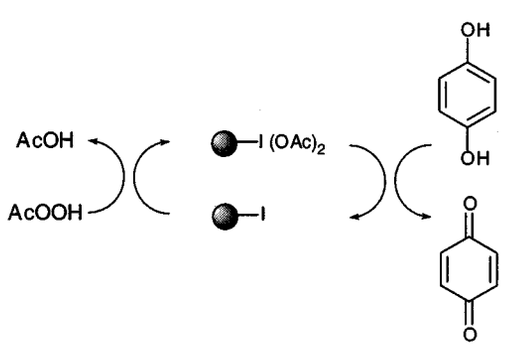
Acyloins are an important class functionality represented in

Table 1 PSDIB oxidative reactions

		R	Yield (%)	NMR and LC Purity (%)
2	**a**	H	Quant.	>95
	b	CO_2Me	Quant.	>95
	c	SPh	Quant.	>95
	d	CH_2OH	Quant.	>95
	e	NHAc	Quant.	>95
6	**a**	H	Quant.	>95
	b	4′-Cl	Quant.	>95
	c	4′-NO_2	Quant.	>95
	d	2′-OMe	Quant.	>95
8	**a**	H	Quant.	>95
	b	4′-Cl	Quant.	>95
	c	4′-NO_2	Quant.	>95
	d	2′-OMe	Quant.	>95
10	**a**	H	84	>95
	b	NHAc	75	90
	c	NHBoc	80	90
	d	NHFmoc	84	>95
	e	NHZ	96	>95

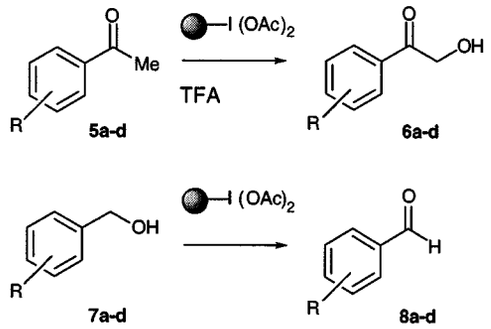


Scheme 2 Preparation of quinones **2a**–**e** a) PhSH (1.0 equiv.), LiCl (1.0 equiv.), HMPA, RT; b) $NaBH_4$, 5 °C, 1 h; c) i) AcCl, Et_3N, DCM, RT, 1 h; then ii) BBr_3, −78 °C, DCM, 1 h; d) see note 9.



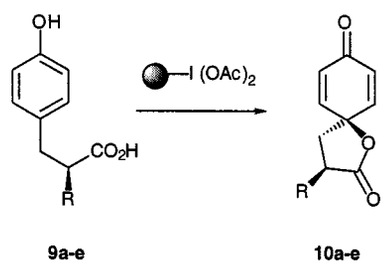
Scheme 3 Regeneration and reuse of the resin.

a large range of natural products.[10] Although indirect methods are commonly used for the α-hydroxylation of ketones we investigated the α-hydroxylation of enolisable ketones under acidic conditions. A series of acetophenones **5a**–**d** were dissolved in a 1 : 1 mixture of DCM–MeCN and at room temperature a stoichiometric amount of the PSDIB resin and TFA were added to give up to 84% conversion to the acyloins **6a**–**d** (Scheme 4). Heating the reaction to 60 °C or adding excess PSDIB resin forced the reaction to completion and afforded the pure 2-hydroxyacetophenones **6a**–**d**, simply by filtration and evaporation (Table 1). The versatility of this reagent was also extended to effect the clean quantitative oxidation of benzylic



Scheme 4 α-Hydroxylation and oxidation of primary alcohols.

alcohols **7a**–**d** to benzaldehydes **8a**–**d** with the best results obtained using excess reagent and/or extended reaction times (Scheme 4 and Table 1). Finally, we have briefly investigated some very useful oxidative spirocyclisation reactions of tyrosine derivatives **9a**–**e** to prepare chiral molecules in a diastereoselective manner in one-step (Scheme 5). Rama Rao,[11] Taylor[12] and



Scheme 5 Oxidative spirocyclisation reactions of tyrosine derivatives **9a**–**e**.

Wipf[13] have all reported similar oxidative cyclisation reactions to afford spirodienones in solution but the yields reported are extremely capricious varying from 18–83% yield. In contrast, using an excess of the new solid supported reagent in DCM–MeCN we obtained the desired product spirodienones **10a**–**e** in consistent yields of 75–96% in greater than 90% purity (Table 1). These compounds are key intermediates in the total synthesis of complex natural products[14] and are useful analogues for further combinatorial decoration.

In summary, an efficient polymer-supported hypervalent iodine reagent (PSDIB) has been used to obtain a range of useful products in clean oxidative reactions in high yield with high purity. We have also demonstrated that the PSDIB consumed in these reactions can be regenerated efficiently with no loss of activity. At present we are employing this reagent in an *in situ* catalytic variant of the reaction and examining its use in multi-step orchestrated synthesis for the preparation of diverse libraries of complex natural products and analogues.

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